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ATVB IN FOCUS:

Calcium, Calcification, Vascular Disease, and Metabolism



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^{18}F -NaF for Imaging Microcalcification Activity in the Cardiovascular System

Evangelos Tzolos, Marc R. Dweck

ABSTRACT: Accumulating preclinical and clinical evidence suggests that calcification is one of the body's primary responses to injury and a key pathological feature of cardiovascular disease. Calcification activity can now be imaged using ^{18}F -NaF positron emission tomography (PET) in combination with either computed tomography or magnetic resonance. These techniques allow visualization of calcification activity and, therefore, provide different information to the established macroscopic calcium imaged with computed tomography. Indeed, ^{18}F -NaF PET has been used to investigate a wide range of valvular conditions, including aortic stenosis, mitral annular calcification, and bioprosthetic valve disease, as well as vascular conditions, including abdominal aortic aneurysm disease, coronary, and carotid atherosclerosis, peripheral vascular disease, and erectile dysfunction. In this brief review, we will focus on how ^{18}F -NaF PET has improved our pathophysiological understanding of cardiovascular calcification and how it can be used as a marker of vascular calcification, providing a useful tool that can be utilized in clinical trials investigating the prediction of both disease progression and clinical events. Finally, we will discuss how ^{18}F -NaF might be employed clinically to improve patient assessment and to guide decision-making.

Key Words: atherosclerosis ■ erectile dysfunction ■ positron emission tomography ■ tomography ■ vascular calcification

Calcification is a key feature of atherosclerosis, heart valve disease, and peripheral vascular disease, that is governed in a highly regulated manner with similarities to skeletal bone formation. Computed tomography (CT), which detects large macroscopic deposits of calcium, has until recently been the only available noninvasive imaging modality allowing visualization of this process.¹ However, imaging of this late stage means that the processes leading to calcium formation have often resolved. There is, therefore, interest in imaging the earlier stages of microcalcification where the disease process is active and therapeutic intervention may be more effective.

Over the last 10 years, ^{18}F -NaF positron emission tomography (PET) has emerged as a noninvasive quantitative imaging modality capable of imaging calcification activity in the vasculature. This has provided significant insight into the underlying pathophysiology of multiple

different cardiovascular disease states and unique information regarding disease activity that may prove clinically useful in the future. In this brief review, we will talk about how ^{18}F -NaF PET works and how this novel approach has been used to investigate a range of valvular and vascular diseases including aortic stenosis, mitral annular calcification (MAC), bioprosthetic valve degeneration, abdominal aortic aneurysm disease, erectile dysfunction, carotid atherosclerosis, and coronary artery disease (Figure 1).

UNDERSTANDING HOW ^{18}F -NAF PET WORKS

CT is currently only able to identify macroscopic deposits of calcium with a diameter between 200 and 500 μm (CT calcium scoring).^{2,3} However, the ^{18}F -NaF signal is higher

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Nonstandard Abbreviations and Acronyms

CT	computed tomography
PET	positron emission tomography
PREFFIR	Prediction of Recurrent Events With ^{18}F -Fluoride

in areas of microcalcification ($<50\ \mu\text{m}$) than macrocalcific deposits for a similar mass of calcium. Newly developing calcium, adjacent or remote from macrocalcific deposits will pass through this microcalcification stage so that ^{18}F -NaF effectively provides a marker of calcification activity, detecting new calcium formation beyond the resolution of CT.^{1,4} Initially used as bone tracer with increased uptake observed in conditions associated with high bone turnover and new bone formation,^{5–7} ^{18}F -NaF demonstrates favorable pharmacokinetic properties and has established an excellent safety profile. Following intravenous injection, roughly 70% of ^{18}F -NaF is plasma-based, with the remaining 30 % found in erythrocytes. Because of its small size and negligible protein binding, one hour after administration only $\approx 10\%$ of the injected ^{18}F -NaF dose remains in the blood ($\text{SUV}_{\text{mean}} [\text{SD}] = 1.13 [0.05]$ in right atrium).^{8–10} The mechanism of ^{18}F -NaF uptake in bone is well understood. First, it diffuses via the capillary network into the bone extracellular fluid, and then it exchanges with hydroxyl groups on exposed regions of hydroxyapatite crystals on the bone surface to form fluorapatite.¹ The intensity of the tracer uptake and as a result of the PET signal depends mainly on 2 factors: the bone blood flow and the surface area of exposed hydroxyapatite.

Hydroxyapatite is also a key feature of vascular calcification, with a growing literature demonstrating that similar mechanisms govern ^{18}F -NaF PET binding in the cardiovascular system. However, here blood flow is likely to be fairly constant, so the surface area of hydroxyapatite appears to be the major factor affecting ^{18}F -NaF uptake. Indeed ^{18}F -NaF binding is highest in areas of microcalcification compared with large macroscopic deposits due to the very high surface area of hydroxyapatite in these regions of powdery microcalcification.^{1,5,6,11} Unlike other PET tracers, ^{18}F -NaF also demonstrates very low uptake in the myocardium, well below that observed even in the blood pool. This important characteristic facilitates clear visualization of regions of increased ^{18}F -NaF uptake in areas of active calcification in the heart but also mediates precise coregistration via alignment of the ventricular blood pools on PET and contrast CT.^{10,12–14}

Validation of the cardiovascular ^{18}F -NaF signal has now been provided in multiple independent studies. Using excised atherosclerotic plaque, Cocker et al¹⁵ demonstrated the association between cardiovascular ^{18}F -NaF PET uptake and the histological staining of hydroxyapatite with Goldner trichrome. Aikawa et al¹⁶ confirmed that ^{18}F -NaF binds predominantly to hydroxyapatite, whereas

Highlights

- ^{18}F -NaF positron emission tomography can be used to study calcification activity across the vasculature.
- It has been used to study (1) coronary artery disease, (2) carotid atherosclerosis, (3) abdominal aortic aneurysm disease, (4) aortic stenosis, (5) bioprosthetic valve degeneration and (6) erectile dysfunction.
- Ongoing clinical trials are evaluating its ability to predict both disease progression and clinical events and to act as a biomarker evaluating drug efficacy.

in the aortic valve, ^{18}F -NaF has demonstrated a close association with areas of tissue with positive histochemical staining for alkaline phosphatase ($r=0.65$; $P=0.04$) and areas with positive immunohistochemical reactivity for osteocalcin ($r=0.68$; $P=0.03$).^{1,17} Irkle et al¹⁸ demonstrated that ^{18}F -NaF binding is increased in regions of microcalcification, rather than large macroscopic deposits. This is predominantly due to surface area effects and because much of the hydroxyapatite crystal is internalized in the center of macroscopic deposit and, therefore, not available for ^{18}F -NaF binding. Creager et al,¹ confirmed that ^{18}F -NaF binds to areas of microcalcification beyond the resolution of x-ray CT and that this binding was proportional to the surface area of hydroxyapatite in a controlled ex vivo model. Recently, Youn et al¹⁹ confirmed ^{18}F -NaF binding to microcalcifications in the coronary arteries as well as the carotids.

In effect, ^{18}F -NaF-PET detects the surface area of hydroxyapatite crystal and, therefore, provides different information to x-ray CT, which detects tissue density. Put another way, ^{18}F -NaF detects microcalcifications and areas of calcification activity, whereas CT detects establish macroscopic deposits of calcium. The difference information provided by ^{18}F -NaF PET compared with CT has now been demonstrated in multiple human studies in vivo across a range of different conditions, as discussed below. However, this observation was perhaps first described by Derlin et al²⁰ in a study of 75 patients undergoing whole-body ^{18}F -NaF PET/CT. They demonstrated that in the aorta, carotids, and femoral arteries, only 12% of all calcified plaques on CT demonstrated increased ^{18}F -NaF uptake, whereas 75% of patients demonstrated increased ^{18}F -NaF uptake remote from calcified CT plaques.

VALVULAR APPLICATIONS

Aortic Stenosis and Bioprosthetic Valve Degeneration

Calcific aortic stenosis is the most common form of valve disease in the Western world and is set to become an increasing health burden with no available effective medical therapy.²¹ The only available treatment for patients that

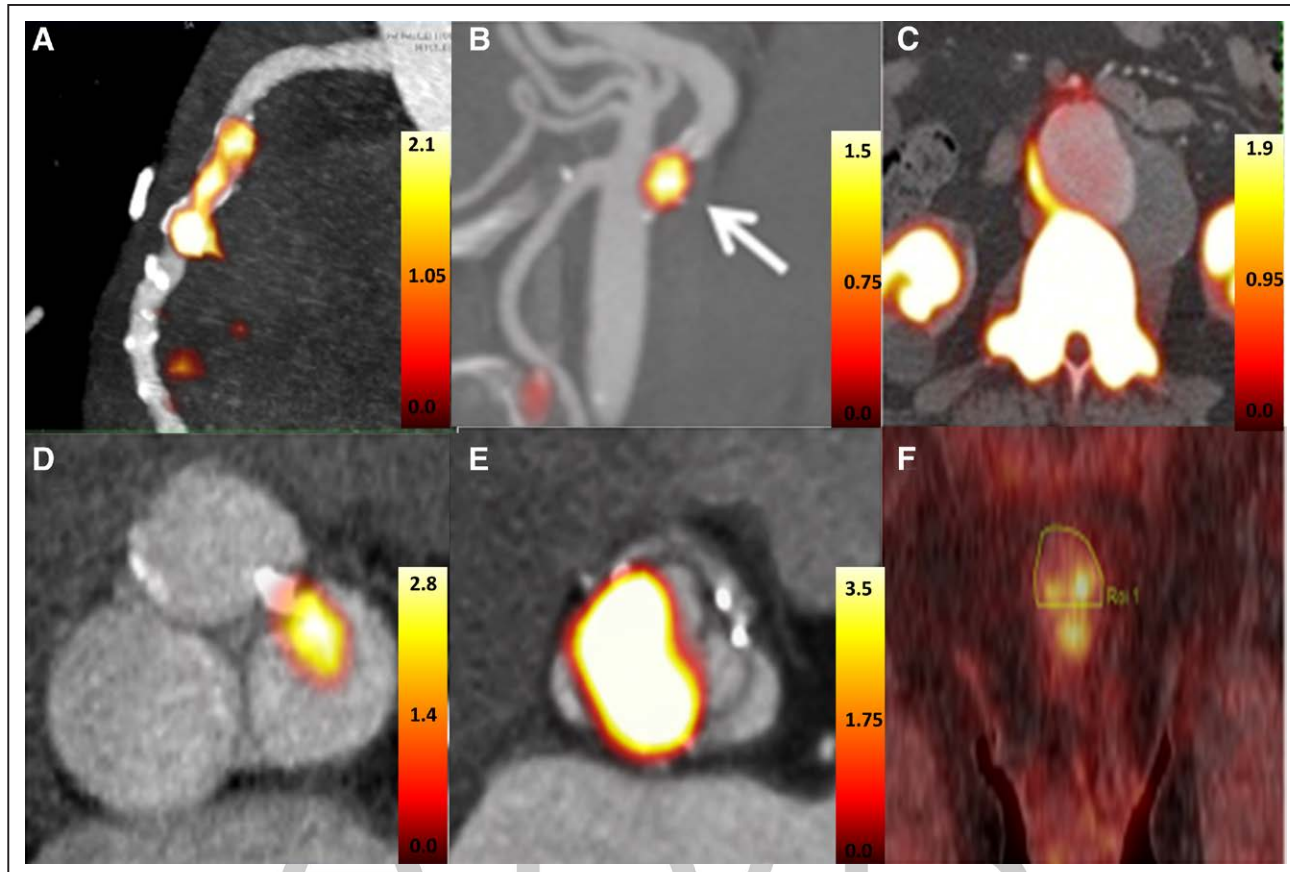


Figure 1. ^{18}F -fluoride uptake in different disease states.

A, Patient with mild aortic valve stenosis and corresponding ^{18}F -NaF uptake in areas of leaflet calcification (image derived from Dweck et al.¹⁷), **(B)** patient with aortic valve degeneration and corresponding ^{18}F -NaF uptake (reprinted from Carlidge et al.²⁹ Copyright ©2019, the Authors), **(C)** patient with abdominal aortic aneurysm (reprinted from Forsythe et al.⁴² Copyright ©2018, the Authors), **(D)** patient with recent myocardial infarction (reprinted from Joshi et al.³⁴ Copyright ©2014, the Authors), **(E)** patient with recent transient ischemic attack and uptake in the culprit carotid artery (reprinted from Vesey et al.³⁹ Copyright ©2014, the Authors), and **(F)** patient with erectile dysfunction and high penile uptake (reprinted from Nakahara et al.⁴⁴ Copyright ©2019, Elsevier).

progress to severe symptomatic aortic stenosis remains surgical or transcatheter aortic valve replacement. There is, therefore, a pressing need to improve our pathophysiological understanding of the disease and to develop effective medical therapies capable of slowing disease progression.^{22,23}

Dweck et al.²⁴ recruited 121 patients with a range of calcific aortic valve disease who underwent both ^{18}F -FDG (a marker of inflammation) and ^{18}F -NaF PET/CT imaging. ^{18}F -NaF uptake activity was higher in aortic stenosis patients than controls and increased progressively with more advanced stages of aortic stenosis. Interestingly increased ^{18}F -FDG activity was also detected, but uptake values were lower than ^{18}F -NaF and had only a mild association with disease severity. Particularly, in the more advanced stages of the disease, calcification, rather than inflammation, had a more predominant role in the disease progression.²⁵ On this basis, we think it should be the target of future therapeutic interventions, although acknowledge that other processes such as fibrosis also determine valve stiffening and progression. Once again, in aortic stenosis, ^{18}F -NaF activity was observed in a

different distribution to the presence of calcium on CT. Moreover, ^{18}F -NaF PET predicted where new areas of calcium on CT would develop on repeat scans performed 2 years later (Figure 2), consistent with it acting as marker of calcification activity and, therefore, providing powerful prediction of disease progression and future aortic valve replacement or cardiovascular mortality.^{26,27}

Calcification also appears to have an important role in bioprosthetic valve degeneration, acting as a major pathological contributor to both progressive bioprosthetic valve narrowing and leaflet tears.²⁸ Carlidge et al.²⁹ examined 15 failed explanted bioprosthetic aortic valves using ^{18}F -NaF PET/CT. All valves demonstrated ^{18}F -NaF leaflet uptake that correlated with microcalcific and macrocalcific deposits within the valve leaflets and colocalized with regions of tissue degradation, pannus, and thrombus on histology. Moreover, they examined 71 patients without known bioprosthetic valve dysfunction. Similar to the ex vivo findings, increased ^{18}F -NaF uptake colocalized with areas of spotty calcification, noncalcific leaflet thickening (suggestive of thrombus), and pannus observed on the

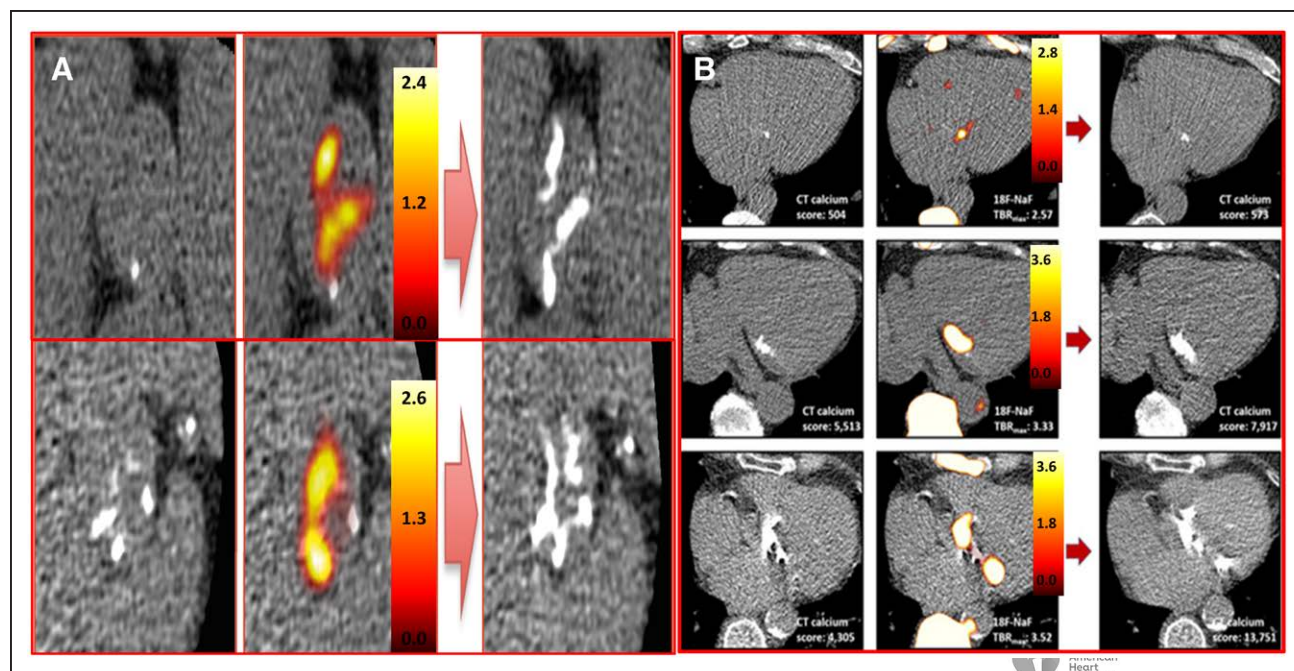


Figure 2. ^{18}F -NaF uptake predicts progression of aortic valve calcification and mitral annular calcification (MAC).

A, Baseline calcium score (left) of 2 patients with aortic sclerosis (top) and moderate aortic stenosis (bottom). Fused ^{18}F -NaF positron emission tomography (PET)–computed tomography (CT) scans (middle) show fluoride uptake in red and yellow. Follow-up CT at 2 y (right) indicated new areas of macroscopic calcium on the repeat CT in a similar distribution to the PET activity (reprinted from Jenkins et al⁴⁷ with permission. Copyright ©2015, the Journal of the American College of Cardiology). **B,** Baseline calcium score (left) of patients with mild, moderate, and severe MAC. Fused ^{18}F -NaF PET-CT scans (middle) show fluoride uptake in red and yellow. Similar to the aortic valve the baseline PET predicts where new macroscopic calcium in the mitral valve will develop on follow-up CT at 2 y (right) (reprinted from Massera et al.⁴⁴ Copyright ©2019, the Authors).

CT. Twenty-four patients with increased ^{18}F -NaF uptake at baseline demonstrated clear evidence of deteriorating bioprosthesis function after 2 years, whereas patients without uptake displayed no change in valve function. Ten patients developed new bioprosthetic valve failure; all 10 patients had increased ^{18}F -NaF uptake at baseline.

Mitral Annular Calcification

MAC is a chronic process, the incidence of which is associated with advanced age, atherosclerosis, and altered mineral metabolism. It can lead to mitral valve dysfunction and is associated with an increased risk of adverse cardiovascular events; however, its pathophysiology remains incompletely understood.^{30,31} Massera et al³² investigated MAC using ^{18}F -NaF and ^{18}F -FDG positron emission tomography. The results were similar to those observed in aortic stenosis. Uptake of both tracers was higher in patients with MAC versus those with normal mitral valves and increased with disease severity. A strong correlation was observed between the baseline CT-MAC score and mitral annular ^{18}F -NaF activity ($r=0.79$, $P<0.001$), whereas a moderate correlation was observed with ^{18}F -FDG uptake ($r=0.32$, $P=0.001$). Similar to the aortic valve, areas of increased ^{18}F -NaF activity on baseline imaging predicted where new regions of macroscopic calcium on CT would develop after 2 years. Indeed, there was a close

association observed between baseline ^{18}F -NaF and the change in CT calcium score ($r=0.75$, $P<0.001$), with ^{18}F -NaF again emerging as a marker of disease activity and predictor of disease progression in this condition.

VASCULAR APPLICATIONS

Coronary and Carotid Atherosclerosis

Dweck et al³³ first described ^{18}F -NaF uptake in the coronary arteries as a novel marker of microcalcification activity in subjects with and without aortic valve disease. Again ^{18}F -NaF provided different information to CT. More than 40 % of patients with high coronary artery calcium scores (>1000 Agatston Units) did not demonstrate increased ^{18}F -NaF uptake, signifying that ^{18}F -NaF might be able to differentiate between active disease and advanced yet burnt out atheroma. Increased ^{18}F -NaF uptake could be localized to individual coronary plaques and notably identified patients with both increased cardiac risk scores and a history of prior cardiovascular events. Joshi et al³⁴ examined 40 patients with stable angina and 40 patients presenting with type 1 myocardial infarction, who all underwent ^{18}F -NaF PET/CT. In the stable cohort, high tracer activity localized to individual coronary plaques in ≈ 40 % of patients. Using intravascular ultrasound and CT, these plaques had multiple adverse, unstable characteristics, including

microcalcification, positive remodeling, and a large necrotic core. In a separate cohort of patients with carotid artery disease undergoing endarterectomy, increased ^{18}F -NaF activity similarly colocalized to carotid plaques with histological adverse plaque features, including increased macrophage accumulation, cell death, and calcification. Finally, in the myocardial infarction cohort, 37 out of 40 patients demonstrated increased ^{18}F -NaF uptake at the exact site of the culprit coronary plaque responsible for the event. By comparison, ^{18}F -FDG was not able to provide similar discrimination of culprit coronary plaques.

Other studies have confirmed the localization of increased ^{18}F -NaF to plaques with adverse characteristics including positive remodeling, low attenuation plaque (<30 HU), spotty calcification, obstructive coronary stenosis, and plaque volumes $>100\text{ mm}^3$ determined by a range of different approaches, including CT, intravascular ultrasound, optical coherent tomography, and histology.^{19,35–37} More recently ^{18}F -NaF PET activity has been associated with increased pericoronary adipose tissue density: an emerging marking of coronary plaque inflammation.³⁸

Outside the heart, Vesey et al³⁹ examined ^{18}F -NaF and ^{18}F -FDG uptake in the carotid arteries after transient ischemic attack or stroke. They recruited 26 patients following a recent cerebrovascular event. All individuals underwent PET/CT scanning using both tracers. ^{18}F -NaF uptake was focal, readily identifiable, and localizable to plaque. The authors detected increased ^{18}F -NaF within culprit lesions responsible for stroke compared with both the contralateral nonculprit carotid artery as well as arteries from patients with nonsymptomatic carotid disease. Similar discrimination was again not provided by ^{18}F -FDG. In a smaller study of 9 patients, Quirce et al⁴⁰ explored ^{18}F -NaF and ^{18}F -FDG uptake in patients with symptomatic carotid stenosis and showed again that ^{18}F -NaF uptake appeared to be higher in the symptomatic carotid, whereas ^{18}F -FDG uptake was nondiscriminatory. Cocker et al⁴¹ examined 11 patients scheduled to have endarterectomy. They performed ^{18}F -NaF PET/CT imaging of the carotid arteries <2 weeks before surgery and established greater ^{18}F -NaF uptake in symptomatic versus nonsymptomatic plaque.

The retrospective identification of culprit plaque is only of limited clinical utility. More interesting is whether ^{18}F -NaF can prospectively identify patients at increased risk of myocardial infarction so that preventative therapies might be instituted to avoid such an event. The prognostic role of ^{18}F -NaF is currently being evaluated in an ongoing prospective multicenter trial: PREFFIR (Prediction of Recurrent Events With ^{18}F -Fluoride; <https://www.clinicaltrials.gov>; Unique identifier: NCT02278211).

Abdominal Aortic Aneurysms, Peripheral Artery Disease, and Erectile Dysfunction

^{18}F -NaF PET has also been explored in patients with abdominal aortic aneurysm disease, peripheral vascular

disease, and erectile dysfunction. In the SOFIA³ study, Forsythe et al⁴² first performed micro-PET-CT and histological analysis of excised abdominal aortic aneurysm disease tissue, establishing once more that ^{18}F -NaF acts as a marker of microcalcification activity. Then they investigated ^{18}F -NaF PET-CT imaging in patients with abdominal aortic aneurysm disease and control subjects. Increased ^{18}F -NaF uptake was observed in the aneurysms compared with areas of nonaneurysmal aorta, providing important predictive information. Aneurysms in the highest ^{18}F -NaF uptake tertile expanded 2.5× more rapidly than those in the lowest tertile. They were also nearly 3× as likely to experience abdominal aortic aneurysm disease repair or rupture. On multivariable analysis, ^{18}F -NaF provided incremental prognostic information over conventional predictors of risk, including aneurysm size. Interestingly, CT calcium scoring was not predictive of either aneurysm expansion nor clinical events.

In peripheral vascular disease, Chowdhury et al⁴³ performed a prospective observational study of 50 patients with symptomatic peripheral arterial disease undergoing ^{18}F -FDG and ^{18}F -NaF PET/CT of the superficial femoral artery before and 6 weeks after angioplasty. The investigators found that both tracers performed well in identifying patients who would develop restenosis within 12 months; indeed, there was clear separation of ^{18}F -NaF activity in patients that did and did not go on to develop restenosis.

Finally, Nakahara et al⁴⁴ investigated ^{18}F -NaF uptake in the penile arteries of prostate cancer patients undergoing clinical PET scans. The investigators demonstrated that ^{18}F -NaF uptake in the cavernous and dorsal penile arteries was associated with the both the presence of existing erectile dysfunction and the probability of its future development. Indeed, penile ^{18}F -NaF activity was 30% higher in patients with compared with patients without erectile dysfunction.

Limitations

PET-CT has grown significantly over the last decade but still faces important challenges. Most notably is the expense of PET imaging, radiation exposure, and the relatively limited availability of this imaging modality. These may limit its widespread clinical adoption, although we note the increasing use of PET in oncology. In addition, there are technical challenges. In particular, PET imaging of the heart is complicated by cardiac, respiratory, and gross patient motion and how this effects image quality, particularly in small structures, such as the coronary arteries. Several motion correction methods have been proposed, leading to novel image reconstruction techniques, and the development of new software that can precisely read fused images. The first approach was to ECG-gate the images and only use PET data acquired in diastole when the heart is still (between 50% and 75% of the R-R interval).¹⁴ Although this improves motion artifact, this approach effectively

ignores three-fourth of the total PET signal leading to increased noise. Doris et al⁴⁵ used an alternative technique that modeled and then corrected for cardiac motion in the PET data using anatomy guided registration algorithm to preserve all of the PET data. Finally, Lassen et al,⁴⁶ used an approach that corrected for cardiac, respiratory, and gross patient motion that in combination with background blood pool corrections markedly improved test-retest reproducibility of coronary ¹⁸F-NaF PET.

Clinical Trials

Although ¹⁸F-NaF PET has provided important pathophysiological insights and emerged consistently as a marker of vascular injury and predictor of disease progression, further work is required to demonstrate the incremental clinical utility of this imaging technique and to justify its relatively high costs. This question is being addressed in multiple prospective studies. As discussed, the PRE¹⁸FFIR Study is a multicenter observational study that will follow ≈700 high-risk patients with coronary artery disease to determine whether baseline ¹⁸F-NaF PET imaging can identify patients at increased risk of future myocardial infarction and disease progression. SALTIRE 2 (<https://www.clinicaltrials.gov>; Unique identifier: NCT02132036) will utilize ¹⁸F-NaF PET to determine if denosumab or bisphosphonate can reduce calcification activity and slow aortic stenosis progression in patients with mild and moderate aortic stenosis.

CONCLUSIONS

¹⁸F-NaF PET provides a marker of calcification activity across a range of cardiovascular conditions, providing potentially useful prediction of disease progression and clinical events. Although the technique has already provided some key pathophysiological insights and is being used as a surrogate efficacy end point in ongoing randomized clinical trials, large prospective studies are required to examine whether it can provide incremental information to justify its more widespread clinical use.

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Disclosures

None.

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